U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-639 / S-045, S-046
Drug Name:	Seroquel (quetiapine fumarate)
Indication(s):	Children and Adolescents Bipolar I mania and Adolescents Schizophrenia
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Keywords: Clinical studies; NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.
In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

1.2 Brief Overview of Clinical Studies

Study D1441C00112 was a 6-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Quetiapine (400 mg/day and 800 mg/day) were investigated in adolescent schizophrenic patients aged between 13 and 17 years. The randomized sample consisted of 222 patients. The primary endpoint was the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

Study D1441C00149 was a 3-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Bipolar I mania patients between the age of 10 and 17 years enrolled in the study. Two hundreds and eighty-four (284) patients were randomized to either quetiapine 400 mg/day, quetiapine 600 mg/day, or placebo in thirty-four United States centers. The primary endpoint was the change from baseline to Week 3 in the Young Mania Rating Scales (YMRS).

Subjects from studies D1441C00112 and D1441C00149 had an option to participate in an open-label, safety and tolerability extension study D1441C00150. Study D1441C00150 is not a subject of this review.

1.3 Statistical Issues and Findings

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of quetiapine as a treatment of adolescent schizophrenia and pediatric and adolescent Bipolar I mania.

According to the sponsor, schizophrenia is a neurodevelopmental disorder that affects many aspects of patient's life. Estimates of the lifetime prevalence of schizophrenia range from 0.5% to 1.5%. While onset of schizophrenia before the age of 13 years is rare, the incidence increases steadily during the adolescent years. Adolescents with schizophrenia have significant impairment, including deficits in cognition, affect, and social functioning.

According to the sponsor, Bipolar Disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive. Approximately 20% to 40% of adults with Bipolar Disorder report onset during childhood. The estimated prevalence among children and adolescents aged 9 to 17 years is 1.2%. Children and adolescents with bipolar mania have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family. Adolescents with Bipolar Disorder have an increased risk of substance-abuse disorders.

Quetiapine (immediate release) was approved for the treatment of adult schizophrenia in 1997 and adult bipolar mania in 2004. The extended release formulation of quetiapine (quetiapine XR) was approved for the treatment of adult schizophrenia in 2007 and adult bipolar mania in 2008. In February 2003, The Food and Drug Administration (FDA) issued a Written Request (WR) asking AstraZeneca to conduct randomized, double-blind, parallel-group, placebo-controlled efficacy studies in schizophrenic patients aged 13 to 17 years and in Bipolar Disorder patients aged 10 to 17 years. Amendments to the WR were issued in May 2004 and February 2005. This submission contains two studies (one schizophrenia and one Bipolar I mania) to fulfill the Written Requests.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\evsprod\NDA020639\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study D1448C00112

3.1.1.1 Objectives

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in the

treatment of schizophrenia in adolescent patients as assessed by the change from baseline to Day 42 in the PANSS total score.

3.1.1.2 Study Design

This was a 6-week, multicenter, double-blind, parallel-group, randomized, placebo-controlled study to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in schizophrenic patients aged 13 to 17 years who were either hospitalized or were outpatients. The study consisted of three periods: a screening and washout period of up to 28 days; a randomized, double-blind treatment period of 42 days; and an optional entrance into a 6-month, open-label study of the safety and tolerability of quetiapine. Subjects were titrated to their assigned doses based on the schedule in Table 1.

Table 1. Study D1448C00112: Quetiapine treatment regimens (mg/day) for administration

		Study day										
Dose group	**Time**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11-42**
400 mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
800 mg	AM	NA	50	100	100	200	200	300	300	400	400	400
	PM	50	50	100	200	200	300	300	400	400	400	400

AM Morning. NA Not Applicable. PM Evening.
(Source: d1448c00112 Study Report; Table 5, page 49)

Patients had to have a PANSS total score of at least 60 at screening and baseline; a score of 4 or greater on at least 1 of the following items: delusions, conceptual disorganization, or hallucinations; and a Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV) diagnosis of schizophrenia. The diagnosis was confirmed by the Schedule of Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (KSADS-PL).

The study was planned for 66 patients per arm to provide 85% power to detect a difference of 15 points change from baseline in the PANSS total score.

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 42 in the PANSS total score. The primary analysis was a mixed effect model for repeated measures (MMRM) with baseline PANSS total score as a covariate, treatment, region, visit, and visit-by-treatment interaction. All effects were considered fixed. An unstructured covariance matrix was used. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows: $P(1) < P(2)$. If $P(2) < 0.05$, then reject null hypotheses associated with P(2) and P(1). Otherwise, if $P(1) < 0.025$, then reject the null hypothesis associated with P(1).

Sensitivity analyses on the primary efficacy variable included an ANCOVA model with missing data imputed by the Last Observation Carried Forward (LOCF) method, and an analysis on the per-protocol sample.

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

The randomized sample consisted of 222 subjects. One hundred and sixty-four subjects (74%) completed the study. The main reasons for dropping out were adverse events, study-specific discontinuation criteria, and patients not willing to continue. Quetiapine groups had higher completion rates than placebo (76.7% and 82.4% compared to 62.7%). There were more subjects dropping out due to adverse events in quetiapine groups than in placebo arm.

Table 2. Study D1448C00112: Disposition of patients

	Placebo (N = 75)	QTP 400mg (N = 73)	QTP 800mg (N = 74)	Total (N = 222)
Discontinued study n (%)	**28 (37.3)**	**17 (23.3)**	**13 (17.6)**	**58 (26.1)**
Adverse event	2 (7.1)	5 (29.5)	7 (53.9)	14 (24.1)
Development of study-specific discontinuation criteria	15 (53.6)	6 (35.3)	2 (15.4)	23 (39.7)
Patient not willing to continue	8 (28.6)	3 (17.7)	3 (23.1)	14 (24.1)
Lost to follow-up	2 (7.1)			2 (3.5)
Other	1 (3.6)	3 (17.7)	1 (7.7)	5 (8.6)
Completed 6-week randomized treatment period	**47 (62.7)**	**56 (76.7)**	**61 (82.4)**	**164 (73.9)**

(Source: d1448c00112 Study Report; Figure 1, page 96)

The demographic and baseline disease characteristics of the modified intent-to-treat sample are presented in Table 3. The average age was 15.4 years. There were more males than females. Sixty-one percent of the subjects were Caucasians. Orientals and Blacks accounted for about 30% of the sample. The average baseline PANSS total score was 96 and ranged from 46 to 165.5. Across three arms, the demographic and baseline disease characteristics appeared balanced.

Table 3. Study D1448C00112: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 73	QTP 400 mg N = 73	QTP 800 mg N = 74	Total N = 220
Age at entry (yr) n				
Mean (SD)	15.3 (1.4)	15.5 (1.2)	15.4 (1.3)	15.4 (1.3)
Median	16	16	16	16
Min – Max	13 – 17	13 – 17	13 – 17	13 - 17
Sex – n (%)				
Male	42 (57.5)	43 (58.9)	44 (59.5)	129 (58.6)
Female	31 (42.5)	30 (41.1)	30 (40.5)	91 (41.4)
Race – n (%)				
Black	11 (15.1)	7 (9.6)	9 (12.2)	27 (12.3)
Caucasian	46 (63.0)	45 (61.6)	44 (59.5)	135 (61.4)
Oriental	12 (16.4)	15 (20.6)	13 (17.6)	40 (18.2)
Others	4 (5.5)	6 (8.2)	8 (10.8)	18 (8.2)
Baseline BMI (kg/m^2)				
Mean (SD)	22.7 (4.7)	21.8 (5.6)	22.5 (4.7)	22.3 (5.0)
Min – Max	15.4 – 40.0	14.5 – 41.3	13.5 – 37.2	13.5 – 41.3
Baseline PANSS-total score				
N	72	73	74	219
Mean (SD)	96.2 (17.7)	96.2 (17.7)	96.9 (15.3)	96.4 (16.8)
Median	94.5	93	93	94
Min – Max	60 – 165.5	46 – 135	69 – 137	46 – 165.5

(Source: d1448c00112 Study Report; Tables 22 & 11.2.1.1.1, pages 100 & 328)

3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The sponsor's primary efficacy analysis is summarized in Table 4. Using the Simes-Hommel's adjustment for multiplicity, both quetiapine 400 mg/day and quetiapine 800 mg/day were statistically significantly superior to placebo.

Table 4. Study D1448C00112: Sponsor's primary efficacy results: change from randomization to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	43	54	55
LS Means	-19.15	-27.31	-28.44
Difference from placebo		-8.16	-9.29
(95% confidence interval)		(-16.06, -0.26)	(-16.22, -2.36)
Unadjusted p-values		0.043	0.009

(Source: d1448c00112 Study Report; Table 25, page 110)

3.1.1.4.3 Sponsor's Other Efficacy Results

Primary sensitivity analyses: Table 5 summarizes the primary efficacy variable analyzed using an ANCOVA model with missing values imputed by the LOCF method. The results corroborated with the primary findings in Table 4.

Table 5. Study D1448C00112: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.52	-25.76	-27.23
Difference from placebo		-7.24	-8.71
(95% confidence interval)		(-14.02, -0.47)	-15.45, -1.96)
Unadjusted p-values		0.036	0.012

(Source: d1448c00112 Study Report; Table 11.2.1.2.3, page 334)
*The sample sizes in Table 5 are larger than in Table 7 at Day 07 due to three subjects who didn't have visits Day 07 and Day 14 assessments (subjects E0004102 and ID0049101 did not have assessment visits Day 07 and Day 14, subject E0340108 did not have assessment visit Day 07).

The results in Table 4 were repeated for the per-protocol (PP) sample. Both quetiapine groups showed a numerical improvement over placebo. However, the differences between each quetiapine group and placebo were smaller and were not statistically significant.

Table 6. Study D1448C00112: Sponsor's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (MMRM) in the PP sample

	Placebo	QTP 400mg	QTP 800mg
Sample size at Week 6	32	44	46
LS Means	-21.28	-26.77	-27.99
Difference from placebo		-5.49	-6.72
(95% confidence interval)		(-14.15, 3.16)	(-14.48, 1.05)
Unadjusted p-values		0.212	0.090

(Source: d1448c00112 Study Report; Table 11.2.1.2.2, page 333)

An analysis on the primary endpoint over time (MMRM):
Table 7 summarizes the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be more consistent for quetiapine 800mg/day dose group than for the quetiapine 400mg/day dose group.

Table 7. Study D1448C00112: Sponsor's efficacy analysis: change from randomization in the PANSS total score (MMRM) over time in the MITT sample

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 07	72	-6.65	73	-8.23	72	-8.80	-1.58	0.410	-2.16	0.214
Day 14	72	-10.09	70	-14.24	71	-16.09	-4.15	0.098	-6.00	0.012
Day 21	65	-12.14	67	-20.37	68	-19.42	-8.23	0.006	-7.28	0.011
Day 28	57	-15.00	59	-22.72	65	-22.38	-7.72	0.023	-7.39	0.018
Day 35	51	-18.00	59	-24.68	62	-26.14	-6.68	0.085	-8.14	0.019
Day 42	43	-19.15	54	-27.31	55	-28.44	-8.16	0.043	-9.29	0.009

(Source: d1448c00112 Study Report; Table 11.2.1.2.1, page 332)
*p-values are not adjusted for multiplicity

Change from baseline in the CGI-Severity of Illness (MMRM):
The change from baseline over time in the CGI-Severity of Illness score was analyzed via an MMRM analysis similar to the primary analysis model. The model included the baseline CGI-S score, treatment, region, visit, and visit-by-treatment interactions. The model utilized an unstructured covariance matrix. The results are summarized in Table 8. The responses did not appear to be consistent for the 400 mg/day dose and did not reach a statistically significant level at the endpoint visit (Week 6). The high dose (800 mg/day) appeared more consistently superior to placebo over time and achieved the 0.05 significant level at Week 6.

Table 8. Study D1448C00112: Sponsor's secondary analysis: change from randomization in the CGI-S score (MMRM) in the MITT sample

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 07	72	-0.18	73	-0.32	72	-0.35	-0.13	0.226	-0.17	0.061
Day 14	72	-0.40	70	-0.56	71	-0.74	-0.17	0.220	-0.34	0.006
Day 21	65	-0.52	66	-0.81	68	-0.78	-0.30	0.065	-0.26	0.060
Day 28	57	-0.64	60	-0.96	65	-0.99	-0.32	0.084	-0.35	0.039
Day 35	51	-0.88	59	-1.10	62	-1.16	-0.22	0.250	-0.28	0.113
Day 42	43	-0.81	55	-1.15	55	-1.28	-0.34	0.104	-0.47	0.018

(Source: d1448c00112 Study Report; Table 11.2.3.2.1.3, page 410)
*p-values are not adjusted for multiplicity

3.1.1.4.4 Reviewer's Results and Comments

This reviewer confirms the findings based on the primary efficacy variable as presented in Table 4. Both doses of quetiapine were statistically significantly better than placebo.

This reviewer performed an analysis based on an ANCOVA model with dropouts imputed by the LOCF method. The model included treatment, region, and baseline PANSS total score. The results were slightly different from those presented by the sponsor in Table 5, but did not affect the outcome of the trial.

Table 9. Study D1448C00112: Reviewer's primary sensitivity analysis: change from randomization to week 6 in the PANSS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Sample size	73	73	74
LS Means	-18.53	-26.09	-27.23
Difference from placebo		-7.55	-8.70
(95% confidence interval)		(-14.26, -0.85)	(-15.37, -2.02)
Unadjusted p-values		0.027	0.011

(Source: Reviewer's results)

Two sensitivity analyses were pre-specified. One was based on the same analysis model as the primary analysis on the per-protocol population. This analysis showed that both doses of quetiapine were numerically better than placebo.

However, the numerical differences did not reach the statistically significant level. The other sensitivity analysis was an ANCOVA model with missing data imputed by the LOCF method. This analysis corroborated with the primary findings. An analysis on the CGI-Severity of Illness score showed superiority of the quetiapine 800mg/day dose group over placebo, but not on the 400 mg/day dose group.

One subject (ID # E0262103) did not appear to have the baseline evaluation or the baseline evaluation visit was miscoded. Removing this subject did not affect the outcome of the study.

Investigator John Gilliam (Site # 10) enrolled 6 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-value = 0.042 for the comparison between quetiapine 400 mg/day versus placebo and p-value = 0.012 for the comparison between quetiapine 800 mg/day versus placebo).

In summary, this study demonstrated the efficacy of quetiapine 400 mg/day and 800 mg/day over placebo on the change from baseline to Week 6 in the PANSS total score. The effect appeared more robust for the 800 mg/day dose group than the 400 mg/day dose group. The 800 mg/day dose group appeared numerically more efficacious than the 400 mg/day; however, the numerical difference was small and did not appear statistically meaningful.

3.1.2 Study D1448C00149

3.1.2.1 Objectives

Primary: The primary objective of this study was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 600 mg/day) with that of placebo in the treatment of Bipolar mania in children and adolescent patients with Bipolar I Disorder, as assessed by the change from baseline to Day 21 in the Young Mania Rating Scale (YMRS) total score.

3.1.2.2 Study Design

This was a 3-week, randomized, double-blind, multi-center, parallel-group, placebo-controlled study. The study was to investigate the efficacy and safety of two fixed doses of quetiapine (400 mg/day and 600 mg/day) and placebo, in divided dosing (either twice daily or three times daily, per the judgment of the investigator). The study consisted of three periods: 1) a screening and washout period that lasted up to 28 days; 2) a randomized, double-blind period of 21 days; 3) an optional entrance into a 6-month, open-label study. Subjects were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups. They could be treated as inpatient or outpatient. Patients initiated the treatment at a 50 mg/day and were titrated to their assigned dosages using the following schedule:

Table 10. Study D1448C00149: Quetiapine treatment regimens (mg/day) for administration twice daily

Dose group	Time	Study day 1	2	3	4	5	6	7	8	9	10	11-21
400mg	AM	NA	50	100	100	200	200	200	200	200	200	200
	PM	50	50	100	200	200	200	200	200	200	200	200
600mg	AM	NA	50	100	100	200	200	300	300	300	300	300
	PM	50	50	100	200	200	300	300	300	300	300	300

AM Morning. NA Not Applicable. PM Evening.
(Source: d1448c00149 Study Report; Table 5, page 49)

Male and female patients between the age of 10 and 17 were eligible to participate in the study. Patients, diagnosed with a DSM-IV Bipolar I mania, had to have an YMRS score of ≥ 20 both at screening and at randomization to enroll. The diagnosis was confirmed by the K-SADS-PL.

The study was planned for 88 patients per arm to provide 85% power to detect a difference of 6 points change from baseline in the YMRS total score.

3.1.2.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 21 in the YMRS total score. The primary analysis was a mixed model for repeated measures (MMRM). Covariates included age stratum, treatment, visit, visit-by-treatment interaction, and baseline YMRS total score. All of these effects were considered as fixed effects. An unstructured covariance pattern was used. Robust variance estimates for the fixed effects were used for testing the treatment differences. The Simes-Hommel's approach was used to control the type I error rate. The procedure ordered the p-values obtained from the pair-wise comparison as follows: $P(1) < P(2)$. If $P(2) < 0.05$ then reject null hypotheses associated with P(2) and P(1). Otherwise, if $P(1) < 0.025$, then reject the null hypothesis associated with P(1).

3.1.2.4 Efficacy Results

3.1.2.4.1 Study Population

The randomized sample consisted of 284 subjects. Seventy-eight percent of the subjects completed the study. The main reason for dropping out was adverse event. There were more adverse events in quetiapine arms than in placebo arm. There were more patients dropping out due to lack of efficacy in the placebo arm than in the quetiapine arms.

Table 11. Study D1448C00149: Disposition of Patients

	Placebo (N = 91)	QTP 400mg (N = 95)	QTP 600mg (N = 98)	Total (N = 284)
Discontinued study: n (%)	**25 (27.5)**	**19 (20.0)**	**18 (18.4)**	**62 (21.8)**
Adverse event	4 (16.0)	15 (79.0)	7 (38.9)	26 (41.9)
Development of study-specific discontinuation criteria	4 (16.0)	1 (5.3)	2 (11.1)	7 (11.3)
Patient not willing to continue	5 (20.0)	1 (5.3)	5 (27.8)	11 (17.7)
Lost to follow-up	2 (8.0)	0 (0.0)	1 (5.6)	3 (4.8)
Lack of efficacy	6 (24.0)	2 (10.5)	0 (0.0)	8 (12.9)
Other	4 (16.0)	0 (0.0)	3 (16.7)	7 (11.3)
Completed 3-week randomized treatment phase	**66 (72.5)**	**76 (80.0)**	**80 (81.6)**	**222 (78.2)**

(Source: d1448c00149 Study Report; Figure 1, page 95 and reviewer's results)

The demographic and baseline disease characteristics of the MITT sample are presented in Table 12. The average age was 13 years old. There were slightly more males than females. Caucasians accounted for about 77% of the sample and Blacks accounted for about 14% of the sample. The baseline YMRS total score was 30 on average and ranged from 12 to 48.

Table 12. Study D1448C00149: Demographic and baseline disease characteristics (MITT sample)

	Placebo N = 89	QTP 400 mg N = 93	QTP 600 mg N = 95	Total N = 277
Age at entry (yr) n				
Mean (SD)	13.31 (2.14)	13.11 (2.16)	13.15 (2.18)	13.19 (2.16)
Median	13	13	13	13
Min – Max	10 – 17	10 – 17	9 – 17	9 – 17
Sex – n (%)				
Male	54 (60.7)	47 (50.5)	55 (57.9)	156 (56.3)
Female	35 (39.3)	46 (49.5)	40 (42.1)	121 (43.7)
Race – n (%)				
Black	12 (13.5)	12 (12.9)	14 (14.7)	38 (13.7)
Caucasian	66 (74.2)	73 (78.5)	73 (76.8)	212 (76.5)
Oriental	1 (1.1)			1 (0.4)
Others	10 (11.2)	8 (8.6)	8 (8.4)	26 (9.4)
BMI at baseline (kg/m^2)				
Mean (SD)	24.14 (5.67)	23.50 (5.31)	23.38 (4.77)	23.67 (5.25)
Min – Max	14.3 – 41.1	12.2 – 38.6	16.2 – 35.2	12.2 – 41.1
*Baseline YMRS-total score**				
N	89	92	95	276
Mean (SD)	30.65 (5.89)	29.45 (5.84)	29.62 (6.35)	29.89 (6.03)
Median	30	29	29	29
Min – Max	21 – 48	12 – 44	20 – 46	12 – 48

(Source: d1448c00149 Study Report; Table 21, page 99)
* Reviewer's results

3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary analysis model was a mixed model for repeated measures with model terms treatment, visit, treatment-by-visit interaction, baseline YMRS total score, and age stratum. Age at entry was dichotomized to two strata: 10-12 years

old and 13-17 years old. According to the statistical analysis plan, randomization numbers 3001-4500 were allocated to 10-12 years old group. Randomization numbers 4501-6000 were allocated to 13-17 years old group. If patients were randomized to a wrong stratum, the patients were analyzed as randomized. The sponsor's primary analysis is summarized in Table 13. Both doses of quetiapine were statistically significantly superior to placebo.

Table 13. Study D1448C00149: Sponsor's primary analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.04	-14.25	-15.06
Difference from placebo		-5.21	-6.56
(95% confidence interval)		(-8.11, -2.31)	(-9.48, -3.65)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 24, page 111)

3.1.1.4.3 Sponsor's Other Efficacy Results

A primary sensitivity analysis (PP): The primary analysis model was repeated using the per-protocol population. The results are summarized in Table 14. This analysis corroborated with the primary analysis presented in Table 13.

Table 14. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (MMRM) in the PP sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	55	60	69
LS Means	-9.60	-15.50	-16.57
Difference from placebo		-5.90	-6.98
(95% confidence interval)		(-9.09, -2.72)	(-10.14, -3.81)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.2, page 368)

A primary sensitivity analysis (LOCF, MITT): An ANCOVA model with missing data imputed by the LOCF method is summarized in Table 15. This analysis also corroborated with the primary analysis presented in Table 13.

Table 15. Study D1448C00149: Sponsor's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.28	-13.42	-15.18
Difference from placebo		-5.15	-6.90
(95% confidence interval)		(-7.93, -2.36)	(-9.66, -4.13)
Unadjusted p-values		<0.001	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.3, page 369)

An analysis on the primary endpoint over time (MMRM): The treatment effects of quetiapine over the duration of the study are summarized in Table 16. The effects appeared consistent over the three weeks of the study. It is noted that many placebo patients did not have Visit Day 04 evaluated.

Table 16. Study D1448C00149: Sponsor's efficacy analysis: change from randomization in the YMRS total score (MMRM) over time in the MITT sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
Visit	n	Mean	n	Mean	n	Mean	Diff	P-value*	Diff	P-value*
Day 04	64	-5.01	81	-8.05	75	-6.84	-3.05	0.015	-1.83	0.120
Day 07	84	-6.78	88	-11.88	90	-11.83	-5.10	<0.001	-5.05	<0.001
Day 14	73	-8.47	79	-13.26	82	-14.76	-4.79	0.001	-6.29	<0.001
Day 21	67	-9.04	76	-14.25	81	-15.60	-5.21	<0.001	-6.56	<0.001

(Source: d1448c00149 Study Report; Table 11.2.1.2.1, page 367)
*p-values are not adjusted for multiplicity

3.1.2.4.4 Reviewer's Results and Comments

This reviewer confirmed the results based on the primary endpoint as presented in Table 13. Quetiapine 400 mg/day and 600 mg/day were statistically superior to placebo in the change from baseline to Day 21 in the YMRS total score.

There were 5 patients who were randomized to a wrong age stratum. The primary analysis was re-analyzed using age group as defined by 10-12 years old versus 13-17 years old. Table 17 summarizes this analysis. Both doses of quetiapine were statistically significant based on this analysis.

Table 17. Study D1448C00149: Reviewer's analysis: change from randomization to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size at Week 3	67	76	81
LS Means	-9.03	-14.25	-15.60
Difference from placebo		-5.23	-6.57
(95% confidence interval)		(-8.13, -2.32)	(-9.49, -3.66)
Unadjusted p-values		0.001	<0.001

(Source: reviewer's results)

The reviewer's ANCOVA analysis with dropouts imputed by the LOCF method deviated slightly from the sponsor's results in Table 15. The deviations did not affect the outcome of the study.

Table 18. Study D1448C00149: Reviewer's sensitivity primary analysis: change from baseline to week 3 in the YMRS total score (LOCF) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Sample size	89	93	95
LS Means	-8.39	-13.63	-15.16
Difference from placebo		-5.24	-6.77
(95% confidence interval)		(-8.01, -2.47)	(-9.53, -4.02)
Unadjusted p-values		<0.001	<0.001

(Source: Reviewer's results)

Investigator John Gilliam (Site # 10) randomized 26 subjects. The results of the primary analysis excluding Site # 10 remained statistically significant (p-values < 0.001 for both dose groups).

In summary, Study D1448C00149 demonstrated the efficacy of quetiapine at 400 mg/day and 600 mg/day in lowering the YMRS total score from baseline at Week 3. The 600 mg/day dose group showed a numerical greater benefit than the 400 mg/day dose group; however, the difference did not appear to be statistically meaningful.

3.2 Evaluation of Safety

Please refer to the clinical review for extensive safety evaluation and report. The following sections explore the effects of quetiapine on body weight and body mass.

3.2.1 Study D1448C00112

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m^2). Repeated measures mixed effect models with baseline body weight or BMI, treatment, region, visit, sex, race, age at entry, and treatment-by-visit interaction as fixed factors were used. The models used unstructured covariance matrices. The results are summarized in Table 19 and Table 20. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

Table 19. Study D1448C00112: Reviewer's exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 07	72	-0.22	73	0.31	72	0.33	0.53	0.014	0.55	0.012
Day 14	72	-0.11	70	1.06	71	0.63	1.17	<0.001	0.74	0.010
Day 21	65	-0.14	67	1.23	68	0.89	1.38	<0.001	1.03	0.003
Day 28	57	-0.35	61	1.40	65	1.05	1.76	<0.001	1.40	0.001
Day 35	51	-0.32	58	1.73	62	1.51	2.05	<0.001	1.83	<0.001
Day 42	44	-0.33	56	1.96	55	1.53	2.30	<0.001	1.86	0.001

(Source: Reviewer's results)

*p-values are not adjusted for multiplicity

Table 20. Study D1448C00112: Reviewer's exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 800mg		QTP400mg - Pbo		QTP800mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 07	72	-0.06	73	0.13	72	0.14	0.19	0.014	0.20	0.017
Day 14	72	-0.03	70	0.38	71	0.22	0.41	<0.001	0.25	0.023
Day 21	65	-0.04	67	0.43	68	0.30	0.47	<0.001	0.34	0.010
Day 28	57	-0.13	61	0.48	65	0.33	0.60	<0.001	0.46	0.003
Day 35	51	-0.11	58	0.56	62	0.47	0.67	<0.001	0.57	0.001
Day 42	44	-0.15	56	0.63	55	0.45	0.78	<0.001	0.61	0.002

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

3.2.2 Study D1448C00149

To explore the effects of quetiapine on body weight and body mass, this reviewer carried out two exploratory analyses. The first analysis was on the change from baseline in the body weight (in kg). The second analysis was on the change from baseline in the body mass index (BMI) (in kg/m^2). The models utilized were similar to the primary analysis model with baseline body weight or BMI as fixed covariates, age group, sex, race, treatment, visit, and treatment-by-visit interaction as fixed factors. The models used unstructured covariance matrices. The results are summarized in Table 21 and Table 22. The results suggested that patients on quetiapine appeared to gain significantly more weights than patients on placebo.

Table 21. Study D1448C00149: Reviewer's exploratory analysis: change from randomization in the Body Weight (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 04	64	0.03	80	0.58	73	0.35	0.55	0.009	0.32	0.060
Day 07	85	0.16	88	0.86	90	0.88	0.69	<0.001	0.71	0.001
Day 14	73	0.13	78	1.31	82	1.29	1.18	<0.001	1.16	<0.001
Day 21	68	0.11	76	1.67	81	1.54	1.56	<0.001	1.43	<0.001

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

Table 22. Study D1448C00149: Reviewer's exploratory analysis: change from randomization in the BMI (MMRM) in the Safety sample

	Placebo		QTP 400mg		QTP 600mg		QTP400mg - Pbo		QTP600mg - Pbo	
Visit	**N**	**Mean**	**N**	**Mean**	**N**	**Mean**	**Diff**	**P-value***	**Diff**	**P-value***
Day 04	64	0.03	80	0.24	73	0.14	0.21	0.012	0.11	0.128
Day 07	85	0.06	88	0.32	90	0.26	0.26	0.001	0.20	0.020
Day 14	73	0.01	78	0.48	82	0.43	0.47	<0.001	0.42	<0.001
Day 21	68	0.00	76	0.56	81	0.48	0.56	<0.001	0.48	<0.001

(Source: Reviewer's results)
*p-values are not adjusted for multiplicity

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study D1448C00112

4.1.1.1 Gender

The primary analysis stratified by gender is presented in Table 23. Quetiapine appeared to improve the PANSS total score for both males and females.

Table 23. Study D1448C00112: Sponsor's primary efficacy results by gender: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Females			
Sample size at Week 6	15	19	19
LS Means	-16.14	-26.05	-25.92
Difference from placebo		-9.91	-9.78
(95% confidence interval)		(-23.03, 3.20)	(-20.75, 1.19)
Males			
Sample size at Week 6	28	35	36
LS Means	-20.78	-27.99	-29.47
Difference from placebo		-7.21	-8.68
(95% confidence interval)		(-17.34, 2.92)	(-17.82, 0.46)

(Source: Reviewer's results)

4.1.1.2 Race

Due to small sample sizes, race was dichotomized to Caucasian versus other races. Quetiapine showed numerical improvements in the PANSS total score in both race groups.

Table 24. Study D1448C00112: Reviewer's primary efficacy results by race: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Caucasians			
Sample size at Week 6	24	33	31
LS Means	-16.79	-23.24	-24.79
Difference from placebo		-6.45	-8.01
(95% confidence interval)		(-16.94, 4.03)	(-17.45, 1.43)
Others			
Sample size at Week 6	19	21	24
LS Means	-25.04	-35.33	-34.99
Difference from placebo		-10.29	-9.95
(95% confidence interval)		(-22.50, 1.92)	(-20.54, 0.65)

(Source: Reviewer's results)

4.1.1.3 Age

Age at entry was dichotomized to ≤ 15 versus > 15 years old. The primary analysis stratified by age at entry is summarized in Table 25. Quetiapine appeared to be more efficacious for subjects under the age of 15 years. For subjects > 15 years old, the relative efficacy of quetiapine versus placebo appeared diminished by the large placebo effect.

Table 25. Study D1448C00112: Reviewer's primary efficacy results by age: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
Age at entry ≤ 15			
Sample size at Week 6	20	23	23
LS Means	-12.18	-28.43	-28.71
Difference from placebo		-16.26	-16.53
(95% confidence interval)		(-28.27, -4.24)	(-26.19, -6.87)
Age at entry > 15			
Sample size at Week 6	23	31	32
LS Means	-25.72	-25.76	-27.91
Difference from placebo		-0.04	-2.18
(95% confidence interval)		(-10.40, 10.32)	(-12.07, 7.70)

(Source: Reviewer's results)

4.1.2 Study D1448C00149

4.1.2.1 Gender

Table 26 summarizes the primary analysis stratified by gender. Treatment benefits were observed in both males and females.

Table 26. Study D1448C00149: Sponsor's primary efficacy results by gender: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Females			
Sample size at Week 3	26	36	31
LS Means	-9.52	-15.27	-14.67
Difference from placebo		-5.75	-5.15
(95% confidence interval)		(-9.84, -1.67)	(-9.53, -0.76)
Males			
Sample size at Week 3	41	40	50
LS Means	-8.64	-13.46	-16.23
Difference from placebo		-4.82	-7.59
(95% confidence interval)		(-8.90, -0.74)	(-11.54, -3.65)

(Source: Reviewer's results)

4.1.2.2 Race

Table 27 summarizes the primary analysis by race. Due to small sample sizes, race was dichotomized into Caucasians versus other races. Treatment effects were observed in both groups.

Table 27. Study D1448C00149: Sponsor's primary efficacy results by race: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Caucasians			
Sample size at Week 3	50	60	60
LS Means	-8.61	-13.72	-15.95
Difference from placebo		-5.10	-7.34
(95% confidence interval)		(-8.42, -1.79)	(-10.74, -3.94)
Others			
Sample size at Week 3	17	16	21
LS Means	-10.82	-16.45	-14.66
Difference from placebo		-5.63	-3.84
(95% confidence interval)		(-11.48, 0.22)	(-9.38, 1.69)

(Source: Reviewer's results)

4.1.2.3 Age

Table 28 summarizes the primary analysis stratified by age groups. Treatment effects were observed in both quetiapine dose groups.

Table 28. Study D1448C00149: Sponsor's primary efficacy results by age: change from baseline to week 3 in the YMRS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 600mg
Age 10-12			
Sample size at Week 3	26	32	37
LS Means	-8.68	-13.49	-17.06
Difference from placebo		-4.81	-8.38
(95% confidence interval)		(-9.73, 0.12)	(-13.05, -3.71)
Age 13 - 17			
Sample size at Week 3	41	44	44
LS Means	-9.35	-14.92	-14.39
Difference from placebo		-5.57	-5.04
(95% confidence interval)		(-9.18, -1.96)	(-8.83, -1.24)

(Source: Reviewer's results)

4.2 Other Subgroups

4.2.1 Study D1448C00112

4.2.1.1 U.S.A. versus non-U.S.A.

The primary efficacy analysis stratified by U.S.A. versus non-U.S.A. is presented in Table 29. Quetiapine appeared to show greater improvement among U.S.A patients than non-U.S.A. patients.

Table 29. Study D1448C00112: Sponsor's primary efficacy results by region: change from baseline to week 6 in the PANSS total score (MMRM) in the MITT sample

	Placebo	QTP 400mg	QTP 800mg
U.S.A.			
Sample size at Week 6	14	15	15
LS Means	-20.69	-38.50	-38.45
Difference from placebo		-17.81	-17.75
(95% confidence interval)		(-33.83, -1.78)	(-32.30, -3.20)
Non-U.S.A.			
Sample size at Week 6	29	39	40
LS Means	-19.33	-22.71	-23.89
Difference from placebo		-3.38	-4.56
(95% confidence interval)		(-11.91, 5.15)	(-11.81, 2.70)

(Source: Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both studies were positive on the primary endpoints. In the Bipolar I mania study, the effects appeared robust for both high dose and low dose. In the schizophrenia study, the effect for low dose appeared weaker and less robust than the high dose. However, in both studies, the difference between the low dose and the high dose was not statistically significant.

5.2 Conclusions and Recommendations

The sponsor submitted two short-term studies to seek claims for the efficacy and safety of quetiapine in the treatment of children and adolescent Bipolar I mania and adolescent schizophrenia. Efficacy in Bipolar I mania was demonstrated by the change from baseline to Week 3 in the Young Mania Rating Scale (YMRS) total score. Efficacy in schizophrenia was demonstrated by the change from baseline to Week 6 in the Positive and Negative Symptoms Scale (PANSS) total score.

In both studies, the point estimate of the high dose was observed to be greater than the point estimate of the low dose; however, the difference between the high dose and the low dose was not statistically significant.

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